REMARKS/ARGUMENTS

Claims 1-11 are currently pending in the above-identified application. Claims 1 and, 4 through 10 have been amended as set forth in detail below. Support for these amendments is identified in the following remarks. No new matter is added by these amendments. In view of the remarks and amendments set forth herein, examination and reconsideration of all pending claims is respectfully requested.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-11 remain rejected under 35 U.S.C. §112, first paragraph, the Examiner believing that the specification, while being enabling for a method of increasing the proliferation of thymocytes in a transgenic mouse, comprising altering the endogenous gene encoding $p27^{kip1}$ of the mouse in the somatic and germ cells of the transgenic mouse, wherein the transgenic mouse does not produce a functional $p27^{Kip1}$, wherein the $p27^{Kip1}$ gene is altered by inserting a nucleotide sequence encoding a positive selectable marker in the endogenous $p27^{Kip1}$ gene, mutation or deletion of the endogenous $p27^{Kip1}$ gene, wherein the transgenic mouse is produced by introducing a plasmid in mouse ES cells and injecting the mouse embryonic ES cells into a blastocyst stage embryo, wherein the plasmid comprises, a $p27^{Kip1}$ gene altered by inserting the nucleotide sequence encoding the positive selectable marker and a nucleotide sequence encoding a negative selectable marker such that the distance between the nucleotide sequence encoding the negative selectable marker and the $p27^{Kip1}$ gene allows homologous recombination between the altered $p27^{Kip1}$ gene in the plasmid and the endogenous $p27^{Kip1}$ gene present in the genome of the mouse ES cells, does not reasonably provide enablement for other embodiments of the claimed invention for reasons of record set forth in the previous office action. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants respectfully do not agree with the Examiner's conclusions as to the unpredictability of the art as it relates to knock-out transgenic non-human animals, the other

bases for the remaining enablement rejections, or the Examiner's summary of Applicants' prior remarks, but in order to further expedite prosecution of certain subject matter encompassed by the claims Applicants have amended claim 1 to recite [a] method for increasing the proliferation of thymocytes in an animal comprising altering an endogenous gene encoding $p27^{Kip1}$ in an isolated thymocyte, or an isolated multipotent cell that differentiates into a thymocyte, of the animal to cause a functional deficiency of cyclin-dependent kinase inhibitor function of $p27^{Kip1}$, introducing the altered cells having the functional deficiency of cyclin-dependent kinase inhibitor function of $p27^{Kip1}$ to the animal thereby increasing the proliferation of thymocytes in the animal. Claim 8 has also been amended to make the terminology consistent with amended claim 1. This amendment is supported by the specification as filed. The Examiner is respectfully directed to, for example, page 17, line 6 through page 19, line 3, page 31, line 30 through page 33, line 30, and the like, wherein methods are provided for increasing the proliferation of thymocytes, T cells, hematopoietic cells, lymphocytes, and the like. The amended claims only encompass *in vitro* or *ex vivo* methods for altering an endogenous gene encoding $p27^{Kip1}$ in a thymocyte or bone marrow. As stated previously, Applicants have demonstrated that cell proliferation, *e.g.*, thymocytes, and the like, can be increased by inhibiting the function of the $p27^{Kip1}$ gene and that because $p27^{Kip1}$ is phylogenetically conserved, both structurally and functionally, the skilled artisan would recognize that this phenomenon can be used to increase cell proliferation in any animal species. Further, Applicants have provided general methods for increasing the proliferation of isolated thymocytes, hematopoietic and bone marrow cells. In addition, copies of US Patents 5,004,681 and 5,192,553 to Boyse *et al.* are provided attached hereto to show that various methods for the collection and re-administration of altered hematopoietic cells, including thymocytes, bone marrow and hematopoietic precursor cells were well known at the time of the present invention.

Applicants believe that the invention as presently claimed is fully enabled by the specification as filed and the Examiner is respectfully requested to reconsider the rejection of claims 1-11 under 35 U.S.C. § 112, first paragraph in view of the amendments and remarks above.

Further, claims 1-11 remain rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons of record set forth in the November 7, 2003 Office Action. In particular, the Examiner believes that the Applicants prior arguments were not persuasive because the claims encompass the making of transgenic non-human animals, which the Examiner believes to be unpredictable. Specifically, the Examiner believes that the effect of altering the expression of an endogenous $p27^{Kip1}$ gene would be unpredictable and therefore an artisan would not be able to predict the phenotype of the animal produced by the claimed methods.

As above, without acquiescing to the rejections and/or reasoning of the Examiner, Applicants have amended claim 1 to more distinctly and clearly point out the present invention. In particular, claim 1 has been amended to recite [a] method for increasing the proliferation of thymocytes in an animal comprising altering an endogenous gene encoding $p27^{Kip1}$ in an isolated thymocyte, or an isolated multipotent cell that differentiates into a thymocyte, of the animal to cause a functional deficiency of cyclin-dependent kinase inhibitor function of $p27^{Kip1}$, introducing the altered cells having the functional deficiency of cyclin-dependent kinase inhibitor function of $p27^{Kip1}$ to the animal thereby increasing the proliferation of thymocytes in the animal. This amendment is supported by the specification as filed. The Examiner is respectfully directed to, for example, page 17, line 6 through page 19, line 3, wherein the invention is described as providing methods for increasing the proliferation of T-cells, hematopoietic cells, lymphocytes, and the like. Generally, the method is described as comprising the steps of a) obtaining cells from a donor; b) treating the cells to eliminate the cyclin-dependent kinase inhibitor function of $p27^{Kip1}$; and c) introducing the treated cells to the recipient. Various methods for eliminating the function of the $p27^{Kip1}$ gene are provided in the specification. Specific details for each step of the various methods are not provided as methods for isolating various blood cells and multipotent cells, and the elimination of the activity of a functional, such as by gene alteration are well known to the skilled artisan. The specification

provides a specific example for eliminating the function of the $p27^{Kip1}$ gene in isolated murine ES cells as well as general methods for the method in other cell types. Applicants also provide attached hereto copies of US Patents 5,004,681 and 5,192,553 to Boyse *et al.* and the references cited therein to provide additional support that methods for isolating and re-administering blood cells, *e.g.*, progenitor cells, were well known in the art at the time of the present invention.

Therefore, Applicants have through various means established that the presently claimed subject matter is described in the specification in such a way as reasonably convey to the skilled artisan that they, at the time of the present invention, were in possession of the claimed invention. Respectfully, Applicants request the Examiner to reconsider the rejection of claim 1-11 under 35 U.S.C. § 112, first paragraph, in view of the above amendments and remarks.

Rejections under 35 U.S.C. §112, Second Paragraph

Claims 4 through 8 remain rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject mater which applicant regards as the invention for reasons of record set forth in the previous office action November 7, 2003. In particular, the Examiner believes that claim 4 is indefinite because the phrase "the gene encoding $p27^{Kip1}$ is altered by insertion of a positively selectable marker" unclear in that a selectable marker is a protein and would not be inserted into a plasmid. Although Applicants believe that the use of the phrase clearly and distinctly sets forth the invention, but in an effort to further expedite prosecution of certain subject matter of the application, claims 4 through 8, 9 and 10 have been amended. In particular, claims 4 through 8 have been amended to recite "selectable marker gene." Claims 9 and 10 were not rejected, but were amended to make them consistent with claim 8 upon which they depend. These amendments clearly set forth that the selectable marker is inserted into the plasmid as a gene (nucleic acid sequence) that encodes a protein. Support for this amendment can be found throughout the specification. In particular the Examiner is respectfully directed, for example, to page 13, lines 26 through page 14, line 13, and page 16, lines 8 through 28. These amendments

are not believed to limit the scope of claims as the amendments merely made to clarify for the Examiner what Applicants believe would be understood by the skilled artisan when the original claim was read in light of the specification.

In view of the amendments and remarks above, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 4 through 8 under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. §102

Claims 1 through 11 remain rejected under 35 U.S.C. §102(e) as being clearly anticipated by Roberts *et al.* (U.S. Patent No. 5,958,769), for reasons of record set forth in the previous office action of November 7, 2003. Applicants do not believe that the present invention is anticipated by Roberts *et al.* Once the investigation into the dates for conception and reduction to practice is completed a Declaration Under 37 C.F.R. § 1.131 establishing that the present invention was either reduced to practice prior to the effective date of Roberts *et al.*, or that the present invention was conceived of prior to the effective date of Roberts *et al.* coupled with due diligence from prior to the effective date to a subsequent reduction to practice or to the filing of the present application, will be submitted shortly.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested. If

the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

Dated: 28 January 2005 By: Brian W. Poor

Brian W. Poor
Reg. No. 32,928

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 94111-3834
Tel: 206-467-9600
Fax: 415-576-0300
BWP:jms
60306011 v1